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Dual Copper- and Photoredox-Catalysed C(sp²)-C(sp³) Coupling

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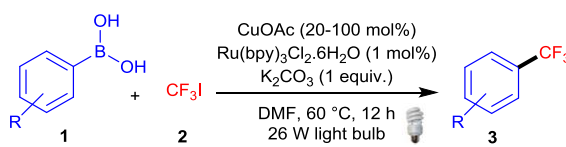
The use of copper catalysis with visible light photoredox catalysis in a cooperative fashion has recently emerged as a versatile means of developing new C-C bond forming reactions. In this work, dual copper- and photoredox catalysis is exploited to effect C(sp²)-C(sp³) cross-couplings between aryl boronic acids and benzyl bromides.

The synergistic combination of transition metal catalysis with photoredox catalysis has in recent years proven itself to be a versatile way to effect C-C cross-couplings.¹ Since its conception, the field has mainly been dominated by methodologies which utilise nickel in synergy with photoredox catalysts, including seminal contributions from Molander and MacMillan, which elegantly demonstrate the synthetic utility of this approach.² Nevertheless, commonly used nickel catalysts in dual-catalysis reactions are toxic and carcinogenic,³ so alternatives with lower toxicity would be beneficial. An emerging, though much less-explored alternative is the use of relatively non-toxic copper salts.⁴ These have an added benefit in that cheap inorganic copper salts can be used, without the need for ligands. For example, Sanford's seminal work in the area uses CuOAc in conjunction with a photoredox catalyst to effect mild trifluoromethylation of aryl boronic acids (Scheme 1A).^{5,6} Nevertheless, a dual-copper and photoredox-catalysed C(sp²)-C(sp³) cross-coupling which involves standard, non-fluorinated C(sp³) centres such as alkyls or benzyls was, surprisingly, yet to be developed.⁷ We therefore set out to explore and develop the first dual copper- and photoredox-catalysed C(sp²)-C(sp³) cross-couplings of aryls with benzylic sp³ centres (Scheme 1B), and its successful development is described herein.⁸

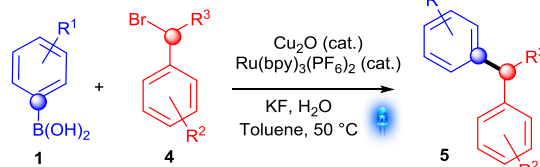
Firstly, a mechanistic design was constructed for the dual copper- and photoredox-catalysed C(sp²)-C(sp³) cross-coupling (Scheme 2). As discussed above, Sanford has shown that

arylboronic acids **1** can undergo transmetallation in dual copper- and photoredox-catalysed systems, providing literature precedence for steps **6**→**I**→**II**.⁵ Additionally, oxidation and reduction potentials from literature support the oxidation of Cu(I) to Cu(II) ($E_{1/2}^{I/II} = -0.161$ V)⁹ by Ru(bpy)₃²⁺ ($E_{1/2}^{*II/I} = 0.77$ V).^{1b} For the sp³ cross-partner, we opted for benzyl bromides **4**, since it has been shown that benzylic radicals **IV** can be generated from electron-deficient benzyl bromides **4** ($E_{red} = -0.95$ V)¹⁰ under photoredox catalysis ($E_{1/2}^{I/II} = -1.33$ V for Ru(bpy)₃²⁺).^{1b,11} Thus, we surmised that **IV** could plausibly react with **II** to form the intermediate **III** and subsequently the desired cross-coupled product **5**, following reductive elimination. At this stage, we envisaged that competing homocoupling of the benzylic radical (from **4**) may be a potential major challenge to successful cross-coupling.

A) Sanford's Seminal Trifluoromethylations:⁵



B) This Work: C(sp²)-C(sp³) cross-couplings



Scheme 1 Dual Copper- and Photoredox-catalysed C(sp²)-C(sp³) Cross-couplings

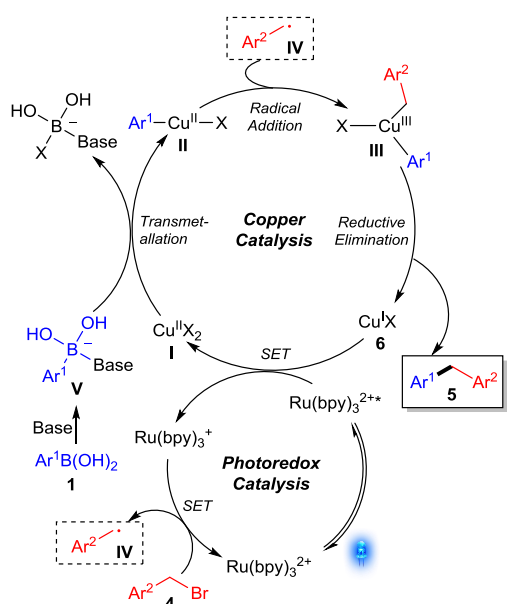
With this proposal in hand, we screened a variety of conditions on model substrates **1a** and **4a** (Table 1, see ESI for full optimisation studies). Initial screens using CuI, Ru(bpy)₃(PF₆)₂ and K₂CO₃, provided our first promising result (10% **5aa**, Entry 1). Subsequent solvent screen (see ESI) identified toluene as the most promising solvent (Entry 2). The yield of desired product **5aa** could be increased from 23% to

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29% by reversing the stoichiometry (**4a** as limiting reagent, Entry 3). Next, a base screen (see ESI) identified KF as the optimum base (Entry 5), while increasing the equivalents of base improves the yield of **5aa** (Entry 6). The counterion of the base appears to have an effect: for example, the use of LiF or NaF resulted in no reaction while NH₄F produced only homocoupled side product **7a** (Entry 4). Further investigations showed that the photocatalyst loading could be lowered to 1 mol% (40% **5aa**, Entry 7). Finally, a screen of copper catalysts (see ESI) identified Cu₂O to be optimal (55% **5aa**, Entry 8). Initial results in Table 1 show that while the yield of the competing homocoupling product (**7a**) appears to remain fairly constant throughout, the yield of desired cross-coupling product **5aa** can nevertheless be successfully optimised to be the major product. Control reactions confirmed that the cross-coupling does not occur in the absence of light, photocatalyst or base respectively and also shows poor reactivity in the absence of Cu₂O (see ESI).



Scheme 2 Mechanistic Design

Up until this point, all optimisation had been carried out using model arylboronic acid **1a**. Much to our surprise and dismay, when any other arylboronic acids **1** were utilised under this set of initial optimised conditions (Entry 8, Table 1), the reaction failed to produce appreciable amounts of cross-coupled **5** and/or suffered from reproducibility issues. Therefore, a second series of optimisation studies had to be carried out in order to develop a set of more general and reproducible conditions (Table 2, see ESI for full studies).

We hypothesised that this unexpected and stark difference in reactivity between different arylboronic acids was due to the corresponding difference in positions of equilibrium between the arylboronic acid and its dehydrated arylboroxine.¹² Since the position of equilibrium is influenced by the presence of water,^{12,13} the addition of controlled quantities of water was screened against phenylboronic acid **1b** (see ESI). From these experiments, we discovered that the addition of 30 equivalents

of water was optimal, improving the yields as well as the reproducibility of the reaction (Entry 3, Table 2).

Table 1 Selected Initial Optimisation Reactions

Entry ^a	Sol.	Base	Ru (mol%)	Cu cat.	4a (%) ^a	5aa (%) ^a	7a (%) ^{a,b}
1 ^{c,d,e}	MeCN	K ₂ CO ₃ (1 equiv.)	2.5	CuI	N/A ^f	10	24
2 ^{d,e}	PhMe	K ₂ CO ₃ (1 equiv.)	2.5	CuI	N/A ^f	23	17
3	PhMe	K ₂ CO ₃ (3 equiv.)	2.5	CuI	28	29	20
4	PhMe	NH ₄ F (3 equiv.)	2.5	CuI	45	0	26
5	PhMe	KF (3 equiv.)	2.5	CuI	13	37	22
6	PhMe	KF (6 equiv.)	2.5	CuI	0	45	28
7	PhMe	KF (3 equiv.)	1	CuI	7	40	26
8	PhMe	KF (4 equiv.)	1	Cu ₂ O	0	55	20

^aDetermined by ¹H NMR analysis using mesitylene as internal standard, 0.1 mmol scale. ^bYields with respect to theoretical maximum formation of **7a**. ^cReaction carried out at R.T. ^dCuI (20 mol%). ^eStoichiometry of **1a/4a** reversed. ^fNot applicable as **4a** is in excess.

Table 2 Selected Further Optimisation Studies

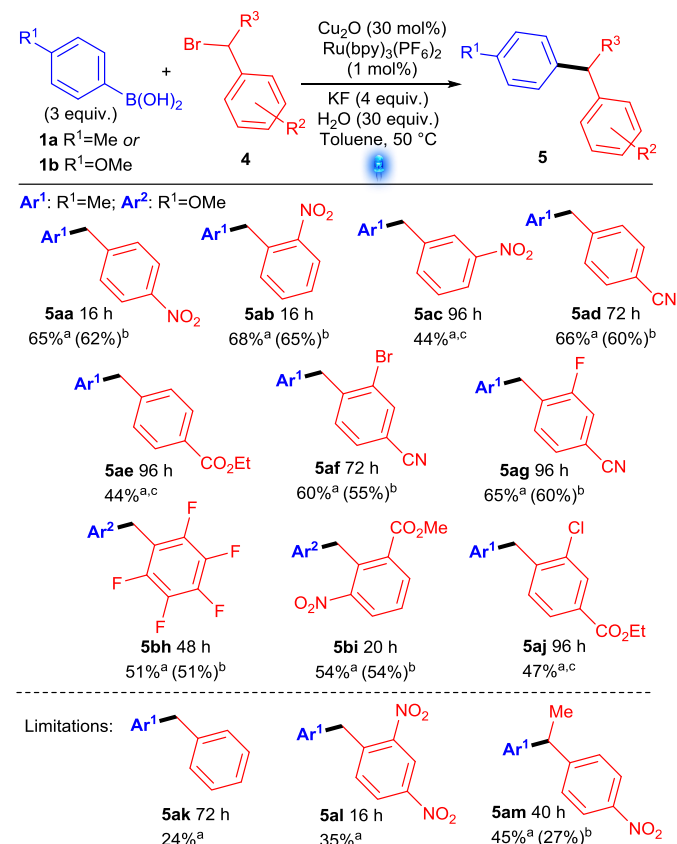
Entry	R ¹	R ²	H ₂ O equiv.	4 (%) ^a	5 (%) ^a	7 (%) ^{a,b}
1	NO ₂	H	0	89	8	4
2	NO ₂	H	20	33	38	16
3	NO ₂	H	30	3	53	28
4	NO ₂	H	40	9	45	22
5	NO ₂	Me	30	3	59	24
6 ^c	NO ₂	Me	30	8	14	22
7 ^{d,e}	NO ₂	Me	30	62	20	10
8	CN	Me	30	41	42	28
9 ^f	CN	Me	30	6	60	30
10 ^{e,f}	CN	Me	30	0	66	34
11 ^e	NO ₂	Me	30	0	65	28

^aDetermined by ¹H NMR analysis with 1,3,5-trimethoxybenzene as internal standard; 0.1 mmol scale. ^bYields with respect to theoretical maximum formation of **7**. ^cIr(ppy)₃ as photocatalyst. ^dFluorescein as photocatalyst. ^eCu₂O (30 mol%). ^f72 h

A number of other photocatalysts were investigated in the reaction (see ESI), including organic dyes, but none were found to be as efficient as Ru(bpy)₃(PF₆)₂ (e.g. Entry 3 vs. Entries 6-7). In order to quickly assess the generality of these conditions, preliminary investigations into the benzyl bromide scope was carried out. In general, it was found that when the benzyl bromide substituent R¹ is less electron-withdrawing (CN vs. NO₂), longer reaction times were required for the reaction to reach completion (Entries 8-9). Finally, increasing the copper catalyst loading to 30 mol% increased the yield of reaction to

66% and 65% for the -NO₂ and -CN substrates respectively and also improved reproducibility (Entries 10 and 11).

Table 3 Benzyl Bromide Scope



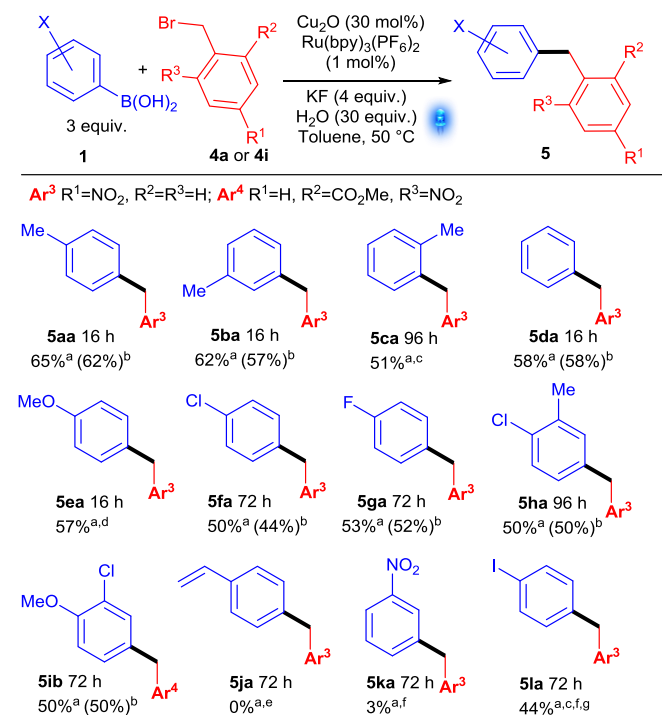
^aDetermined by ¹H NMR analysis of the crude product using 1,3,5 trimethoxybenzene as an internal standard. ^bIsolated yield. ^cIsolated yields not available due to co-elution with unreacted 4.

With a more general optimised protocol in hand, our attention turned to investigating the benzyl bromide substrate scope (Table 3). It should be noted that electron-deficient benzyl bromides, which have lower reduction potentials than their electron-rich counterparts,¹⁴ have previously been required for efficient benzyl radical IV formation under photoredox catalysis.¹¹ Consequently, strongly electron-withdrawing substituents (e.g. NO₂) are tolerated well in the *para* and *ortho* positions, furnishing the corresponding products **5aa** and **5ab** in good yields (62% and 65%). However, when the NO₂ substituent is moved to the *meta* position (**5ac**), the reaction becomes sluggish and the yield is modest even at prolonged reaction times (44%, 96 h). The sluggish reaction with **4c** is consistent with the higher reduction potential¹⁴ of benzyl bromide **4c** (vs. **4a-b**) as NO₂ exerts a smaller withdrawing effect in the *meta* position. Increasing the reaction time allows for the use of benzyl bromides bearing more moderately electron withdrawing substituents (e.g. CN and ester groups), furnishing the desired products **5ad** and **5ae** in good and moderate yields respectively (60% and 44%). Halogenated benzyl bromides are also good substrates providing products **5af** and **5ag** in yields of 55% and 60% respectively. The selectivity in activating the C(sp³)-Br bond preferentially over the C(sp²)-Br bond (**5af**) is significant as it renders this protocol orthogonal in reactivity to traditional palladium cross-couplings and provides a platform for

further functionalisation. This protocol also tolerates highly fluorinated moieties, giving the product **5bh** in 51% yield. Substrates bearing a mixture of various electron-withdrawing groups are also tolerated, furnishing the desired products **5bi** and **5aj** in moderate yields. In particular, the formation of **5bi** highlights that the reaction is tolerant of steric hindrance on the benzyl bromide substrate.

As expected, attempts to expand the scope beyond electron-poor benzyl bromides proved challenging due to the higher reduction potentials, with benzyl bromide **4k** providing only 24% yield of desired product (**5ak**) despite extended reaction times (72 h).¹⁵ Surprisingly, reducing the reduction potential even further (e.g. by having two electron-withdrawing nitro groups) does not necessarily improve the cross-coupling (35% **5al**), due to competing protodebromination of starting material **4l** (31%). Secondary benzyl bromide **4m** successfully cross-couples, albeit less efficiently than its primary counterpart under these conditions (**5am** vs. **5aa**). Having ascertained the substrate scope and limitations, we proceeded to demonstrate that the reaction can be successfully scaled up to 1 mmol, albeit with a slightly reduced yield and increased reaction time (51% **5aa** after 96 h, see ESI).

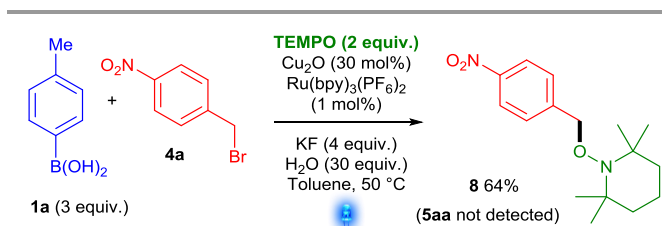
Table 4 Arylboronic Acid Scope



^aYield determined by ¹H NMR analysis using 1,3,5 trimethoxybenzene as an internal standard. ^bIsolated yield. ^cIsolated yields not available due to co-elution with unreacted 4. ^dIsolated yields not available due to co-elution with homocoupling product. ^e**1j** consumed to form insoluble polymers. ^fPoor solubility of arylboronic acid. ^gUsing boroxine instead of boronic acid, portionwise addition.

The arylboronic acid scope was investigated next (Table 4). Electron-rich tolylboronic acids perform well as substrates, furnishing the desired products **5aa-5ca** with a slight and gradual reduction in yield when moving from *para* (62%) to *meta* (57%) to (51%) *ortho*, presumably reflecting the gradual increase in sterics. Unsubstituted phenylboronic acid **1d** and electron rich *p*-anisylboronic acid **1e** also proved to be good coupling partners, yielding products **5da** and **5ea** in 58% and 57% respectively. Electron-

withdrawing substituents are also tolerated in the reaction, with **5fa** and **5ga** formed in 44 and 52% respectively. Arylboronic acids bearing a combination of electron-withdrawing and electron-donating groups are also amenable to the coupling conditions: **5ha** and **5ib** are formed in 50% yields. Unsurprisingly, alkene moieties, which are liable to react with intermediate radicals, are not tolerated (e.g. **5ja**). Although the reaction is tolerant of both electron-rich and electron-poor arylboronic acids, some arylboronic acids, especially ones containing highly polar substituents (e.g. NO₂) suffer from poor solubility in the reaction mixture, which detrimentally affects their ability as coupling partners (**5ka**). Any polar groups such as NO₂ are thus best introduced *via* the benzyl bromide coupling partner instead. In some cases, such as with **5la**, the solubility problem can be partially overcome by utilising the arylboroxine (44% **5la**).



Scheme 3 Radical Trap Experiment

Having investigated the scope of both coupling partners, preliminary mechanistic investigations were conducted next. Carrying out the reaction under our optimised conditions in the presence of known radical trap TEMPO results in complete inhibition of the reaction, with no observed formation of desired product **5aa** (Scheme 3). In addition, the TEMPO trapped benzylic radical adduct **8** can be isolated in 64% yield. This result supports our hypothesis that the mechanism is radical based and most likely involves benzylic radicals **IV** as intermediates. Experiments to determine the quantum yield of the reaction were also carried out (see ESI). The quantum yield of the reaction was calculated to be $\phi = 0.012$, which rules out the presence of any radical chain mechanisms in the reaction.¹⁶

In conclusion, we have successfully developed the first dual copper- and photoredox-catalysed C(sp²)-C(sp³) cross-couplings of aryls with benzylic sp³ centres. Surprisingly, addition of water was found to be necessary for the generality and reproducibility of the reaction, thereby allowing the successful cross-coupling of a variety of arylboronic acids with electron-deficient benzyl bromides.

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